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CLINICAL EXPERIENCE WITH KOGA'S CYANOCUPROL.

By T. I. Masuda, M.D.,

ISHIGAMI HOSPITAL, TENNOJI, OSAKA,

AND

T. K. Matsuda, M.D.,

ISHIGAMI SANITARIUM FOR CONSUMPTIVES, HAMADERA, NEAR OSAKA.

The problem of tuberculosis therapy is one of the most absorbing and elusive in medicine. Koch's epoch-making invention of tuberculin was accepted at first with the greatest interest not only by the medical profession, but by those who were suffering from the disease. Its therapeutic value, however, was not as great as anticipated, while, on the other hand, so many disadvantages were detected in the form of so-called reactions that it finally came to be considered not only useless but actually injurious, and its clinical application was practically given up. Subsequently many improvements were attempted by Koch himself and many others until more than forty preparations have been reported, none of which seems to be either efficacious or entirely free from harmful reactions.

Since Ehrlich and Hata obtained such brilliant success in the treatment of syphilis with salvarsan many attempts have been made to discover a remedy for the treatment of tuberculosis on similar principles. In April of last year, at the annual meeting of Kenkyusho Dosokwae (Association of the Fellowship of Kitasato Institute for Medical Research), Dr. Koga read a paper reporting the success in animal tests as well as in the clinical application of his own antituberculosis remedy. The new preparation, which has been named cyanocuprol, is the compound salt of potassium cyanide with copper (as may easily be inferred from the name), the exact chemical composition of which has not yet been reported. He began his experiments with potassium cyanide, and he found that in some animals its use resulted in a distinct healing tendency. In most cases, however, the destructive process was most evident because of the strong toxicity of the drug. He experimented further, trying to prepare some other compound which would be more effective and less poisonous. The new preparation which he succeeded at last in making was suggested by Koch's "aurum kalii cyanatum" and Linden's copper compound. After several series of animal tests, he concluded:

1. That guinea-pigs previously inoculated with tubercle bacilli and then treated with this preparation do not die of the infection or at least their lives are prolonged in comparison with the control animals.

2. That the drug has considerable healing ability, as shown by the condition of the affected organs at autopsy and by subsequent histological study. There is marked influence in the stimulation of formation of new tissue from surrounding parts, and the tubercle bacilli contained in them are in some instances entirely killed. Inoculations with pieces of such organs into healthy animals cause no tuberculous process.

3. That the injection of the drug, if begun at the time of inoculation or within four days from it, does not prevent the onset of tuberculosis. After the formation of nodular tubercles, however, it begins to manifest its influence upon them.

4. That some signs of reaction are constantly observed after the injection in the form of local hyperemia and infiltration of round cells, followed finally by proliferation of fibroid tissue (encapsulation).

5. That too large doses are distinctly harmful, because a softening of the tubercles and a generalization of the process is caused and the animal dies.

From the foregoing statements we may assume that the preparation is by no means germicidal, except in a secondary way. It shows little parasitropic nature, while the organotropic property seems to be great, and so it may not be called a strictly chemotherapeutic remedy, according to Ehrlich's definition. Yet a favorable influence is experimentally proved with certainty.

Koga proceeded further to apply this remedy to 125 patients. The results are shown in the following table:

	Number of patients.	Cured.[1]	Improved.[2]	Died.	Treatment discontinued.	In course of treatment.
Passive cases:						
1st stage . . .	19	13	2	0	1	3
2d stage . . .	6	3	3	0	0	0
3d stage . . .	4	1	3	0	0	0
Active cases:						
1st stage . . .	7	4	2	0	0	1
2d stage . . .	11	3	5	0	1	2
3d stage . . .	8	0	3	3	0	2
Surgical tuberculosis	8	1	4	0	2	1
Total . . .	63	25	22	3	4	9

LOCAL REACTIONS. On the day after injection a slight dulness and rales appeared over the affected spot, where no such physical symptoms were evident before the injection, or if such signs were present, they increased in degree and extension. In from seven to nine days the reactions disappear.

In cases of skin tuberculosis the affected parts become reddened and swollen, painful to pressure, and sometimes suppurative. After ten days this reaction entirely disappears. In 5 cases of glandular tuberculosis the swollen glands became painful and the swelling increased. The pain and swelling gradually decreased after five days until the glands were somewhat smaller than before. On the next injection they again became painful and swollen, but less intensely than before, and after from five to seven injections they were completely absorbed. In 1 case the suppurating gland broke through to the surface of the skin, but healed without leaving behind a fistula. In 1 case of renal tuberculosis the kidney became swollen and painful, hematuria followed on the day after injection, and the general condition became worse, but in seven days all symptoms gradually decreased. The pain at the time of urination diminished and the turbid urine became clear and transparent.

All of these reactions were much less intense in patients who had been treated previously with tuberculin.

TUBERCLE BACILLI IN SPUTUM. Of 8 patients of the second and third stages the sputum was examined every day, with the following result: From the day after injection the number of bacilli was gradually increased, reaching the maximum point on the fourth or sixth day, when it began slowly to decrease. After from seven to ten days the number was obviously smaller than before the injection, and after repeated injections the bacilli disappeared entirely in favorable cases. Morphologically the bacillus undergoes striking change. In one to three days after the injection the coloring of some bacilli became fainter and homogenized, granular construction was lost, and some were cut into pieces and in appearance resembled streptococci or staphylococci.

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[1] Body temperature constantly below 37° C. Absence of clinical symptoms. Patients are able to go on with their work without trouble.

[2] Symptoms much reduced but not entirely absent.

FEVER. In some cases, at the first and second injections, the temperature rose to 38° to 40° C. after several hours, then fell gradually to normal in three to seven days. Among 10 highly feverish patients 3 became afebrile after the first injection, 3 after the second, and 3 after the third, while 1 case was entirely unaffected. In all other cases no influence was evident.

BODY WEIGHT. In most cases the body weight decreased (500 grams or more) immediately after the injection, only to be almost restored in a few days or in two weeks at the latest. In exceptional cases the body weight increased a little after the first injection.

SUBJECTIVE SYMPTOMS. Cough and expectoration are usually relieved after the injection and the patient feels fairly comfortable.

ACCESSORY ILL EFFECTS. No remarkable symptoms may be noticed as accessory ill effects of the remedy itself. Sometimes if the solution is injected too rapidly the patients complain of an uncomfortable feeling on the chest and of palpitation of the heart immediately after the injection. In most cases night-sweats are complained of for two or three days after the injection.

DOSES. As shown in the animal experiments too large doses are injurious. The doses suggested by Koga are as follows:

For incipient cases, 7 to 9 c.c.
For advanced cases, 6 to 7 c.c.

Doses should be given intravenously and repeated five to ten times at intervals of two weeks or more. This interval was proved most satisfactory by animal tests. It should never be shortened.

CONTRA-INDICATION. The treatment is contra-indicated for those in whom the respiratory surfaces are too much affected or the general condition too seriously weakened.

EFFECT OF OTHER DRUGS ADMINISTERED DURING TIME OF TREATMENT. Aq. lauroc., creosote, guaiacol, and iodin preparations should not be used during treatment with cyanocuprol.

Koga's paper was received with great interest. He was unwilling, however, to offer the remedy immediately for public use, but felt that it should be tested further on the sick bed, not only by himself but by many other skilled practitioners, in order that an impartial estimate might be made of its therapeutic value and that the details of its practical application might be thoroughly worked out. For the purpose of this investigation twenty well-known hospitals and sanatoria were asked, in the name of Prof. Kitasato, the president of the institute, to try this preparation on the sick bed. Accordingly, we began to use it in May, 1915, and up to the end of 1915 about two hundred patients had been treated. We collect here a record of the experiments of this period and will report the general result. Of course this period of half a year is too short to make any definite statement, especially with regard to the therapeutic value of a preparation for a chronic disease like tuberculosis, the total course of which may extend over several years. What is said here, therefore, is necessarily of temporary validity. Whether this result may be of ultimate value can be decided only by further observations.

We may summarize the total results in the following table:

TOTAL NUMBER OF PATIENTS TREATED.

	At Tennoji.	At Hamadera.
1st stage	17	21
2d stage	36	57
3d stage	23	29
	76	107

TOTAL RESULTS OF THE TREATMENT.

AT TENNOJI.

	1st stage.		2d stage.		3d stage.		Total.	
	No. of patients.	Per cent.	No. of patients.	Per cent.	No. of patients.	Per cent.	No. of patients.	Per cent.
Cured	10	58.8	9	25.0	0	0	19	25.0
Much improved	6	35.3	20	55.5	6	26.1	32	41.2
Somewhat improved	1	5.9	5	13.9	14	60.9	20	26.4
Remaining unchanged	0	0	0	0	2	8.7	2	2.6
Worse	0	0	1	2.8	1	4.3	2	2.6
Treatment discontinued	0	0	1	2.8	0	0	1	1.3
	17	..	36	..	23	..	76	

AT HAMADERA.

	1st stage.		2d stage.		3d stage.		Total.	
	No. of patients.	Per cent.	No. of patients.	Per cent.	No. of patients.	Per cent.	No. of patients.	Per cent.
Cured	16	76.4	9	15.8	0	0	25	23.4
Much improved	4	19.1	28	49.1	4	13.8	36	33.7
Somewhat improved	1	4.8	16	28.7	19	65.5	36	33.7
Remaining unchanged	0	0	1	3.5	3	10.3	4	3.7
Worse	0	0	0	0	2	6.9	2	1.8
Treatment discontinued	0	0	3	5.4	1	3.4	4	3.7
	21	..	57	..	29	..	107	

The stage is decided upon by a comparison with the standard given by the Bureau of Hygiene of Germany.

Cured: No fever, objective and subjective symptoms absent, and patients are able to go on with their work without feeling any inconvenience. No bacilli found in the sputum.

Much improved: Only slight objective symptoms remain. Patients subjectively quite well. Sputum may contain bacilli.

Somewhat improved: Subjective disturbance diminished. Objective symptoms somewhat reduced. Fever may continue.

Worse: Objective symptoms become noticeably worse after injection, or subjective symptoms seemed aggravated. These may not necessarily have been the direct result of the injection.

NECESSARY PRECAUTIONS BEFORE INJECTION. As the toxicity of the remedy is very great it is absolutely necessary to have the patients under constant observation and control, and consequently they should be treated in hospitals only. Good results could never be obtained, we are sure, with ambulant treatment, for many serious and unexpected accidents may occur, especially when patients have a tendency to hemoptysis. In the case of patients suspected of intestinal tuberculosis, special attention should be paid to the evacuation of the bowels in order to avoid violent reaction. To secure complete and regular evacuations we used magnesium sulphuricum or some other like saline laxatives. Enemas were also used.

TREATMENT AFTER THE INJECTION. At first we required of all patients absolute rest for three days and nights after the injection, according to the instructions of Koga, but as this was sometimes quite unendurable, especially by those who had no very marked symptoms, we afterward changed the requirement to twenty-four hours of absolute rest, allowing them to sit up in bed during the following forty-eight hours at the time of meals and during urination and defecation. No ill effects followed this practice. This is only a general rule, however, and should be properly modified according to the condition of the individual patient. It is best to require during the three-day period, however, a half-fluid diet (rice mush), in order to avoid the irritating reaction in the bowels which very often takes place, especially in cases of intestinal tuberculosis or in patients who have chronic digestive disturbances.

DOSES. The amount injected must, of course, be regulated according to the condition of the patients, but in general we used far smaller doses than those employed by Koga. At first we gave exactly as much as prescribed, but after some experience we found the dose too great and reduced it, and since then various unpleasant reactive phenomena, which formerly had been frequent, have usually been avoided. The doses which we used are as follows:

For patients in the first stage, 5 to 6.5 c.c.
For patients in the second stage, 3 to 4 c.c.
For patients in the third stage, 2 to 3 c.c.

Special attention was given to dosage in cases which gave a history of repeated or recent hemoptysis. In such cases, even if they were not much advanced, 2 to 3 c.c. were usually given as the first dose, and the amount given at further injections was determined in accordance with the observed effects of this amount. When suitable doses were found the same were kept constant for some time. We found that we had to be very cautious in using increasing doses of the drug, just as with tuberculin, in order to avoid such unpleasant events as hemoptysis, which may take place on the third to fifth injection. At any rate it is absolutely necessary to take into careful consideration the individual constitution and the stage of progress of the disease in each patient and having determined the most suitable dose to continue it throughout the treatment. If the chief symptoms have almost disappeared it is sometimes well to reduce the quantity in the two or three last injections. Otherwise the symptoms may be aggravated rather than entirely removed.

LOCAL REACTION. According to Koga's report the local reaction is more or less noticeable after every injection. Dulness and rales may increase both in intensity and extent. This reaction is proportionate to the healing effect to some extent, *i. e.*, the greater the reaction the greater the healing effect. We first thought, therefore, that the reaction was a manifestation of the healing process, and that consequently that dose should be given which would cause some definite reaction. We found afterward, however, that the healing process and the reaction did not always go hand in hand, and that, on the contrary, the greatest healing effect was accompanied by the least reaction. Therefore we reduced the size of the doses so that the reaction might be avoided as nearly as possible.

As typical reactive symptoms we may count the follwoing signs: On the first or second day after the injection the increase of rales is more or less marked, accompanied by cough and expectoration. At first, when larger doses were given, this exaggeration of symptoms was present at almost every injection, but even at that time the increase of dulness was not always noted, as recorded in Koga's report. With the reduction of dosage this reaction is wanting in most cases. Sometimes the multiple rales, which persisted against all treatments, disappear at once, the dulness is wonderfully lessened, becoming somewhat tympanitic in tone, and the breath sounds become bronchial. These no doubt show that pneumonia-like changes are taking place. It is noteworthy that sometimes at the spot where dulness existed tympany appears and persists for one or two days while all other symptoms remain quite unchanged.

These reactive signs come out in a great majority of cases on the day after injection, and only in rarer cases on the second and third days. Sometimes they may occur only after from five to seven days, and in such cases the result seems generally to be bad. They do not persist for more than two or three days and are removed usually by keeping the patients at rest without giving any special treatment. At times we obtained a marked sedative effect by the intravenous injection of calcium chloride, 5 per cent. solution. In general the reaction is more marked with large doses and more striking in the more advanced cases.

It is possible that the remedy may stimulate or arrest the process according to the severity of the disease perhaps or the size of the dose. But as there can be no reason that the same agent may have on the same organ or tissue at the same time two quite opposite effects so this apparent paradox should be explained. What seems to be inhibitive is not actually so, but the original effect is of a stimulating nature. When the dose is too small the effect of stimulation lasts for a very short time and soon runs into a period of arrest. Koga's assumption that the reaction itself is the manifestation of the healing process is supported by this explanation. It seems then that the secret of success with this treatment lies in choosing the most efficient dose, which varies with every individual. In this respect the remedy bears a great resemblance to tuberculin.

After the first period of stimulation, at the beginning of the period of arrest, all reactive symptoms become less marked, and the preëxisting dulness, rales, etc., are diminished in most cases. Especially is this true in relatively early cases, when dulness and rales disappear, expiration is no longer prolonged, and in areas in which the breath sounds had weakened or totally vanished, they may be heard again only after two or three successive injections. The disappearance of the dulness is most noteworthy. An effect so marked and so immediate has not been observed with any other remedy. In chronic cases, on the other hand, it is specially difficult to effect a total disappearance of the dulness.

We have avoided injecting patients who are suffering from early pleuritis, fearing that a violent reaction such as Koga described might possibly follow. In chronic cases of pleuritis, however, we have seen the pain and friction rub come out again, or the whole inflammatory process become active, accompanied by fever, pain, and renewed accumulation of exudation, etc. But this was found only in a few cases. In the great majority of cases no marked effect was observed.

INTESTINAL TUBERCULOSIS. It is a well-known fact that cyan preparations possess great affinity for the bowels, and bleeding and submucous hemorrhage have often been observed in animals treated with cyan compounds. Clinical experience corresponds with these observations. Even if the bowel contents were carefully washed out as prescribed, and all possible means used to lessen the reaction, we found patients with intestinal tuberculosis who complained of uncomfortable feeling in the bowels, peristaltic unrest and pain, etc., after the injection. At Hamadera one patient discharged a bloody and mucous stool (dysenteric) after the injection. Recovery from this condition was very slow. These reactions may be avoided to a certain extent by evacuating the intestines, as emphatically recommended by Dr. Otani (chief of the clinical department of Kitasato Institute), and by giving smaller doses.

In one case of intestinal tuberculosis we saw a paroxysm of severe gastralgia after every injection, with no particular change in the stool. Another case of gastralgia came on a few hours after the injection in a patient who disobeyed our orders and ate an ordinary meal of boiled rice and some pieces of persimmons. As the patient had complained at two preceding injections of oppression of the stomach this attack of gastralgia may be explained as irritation caused by the injection and aggravated by the alimentary stimulation. The example goes to show how important it is to pay special attention to the diet. The same caution should be used in cases of simple bowel catarrh of acute or chronic nature. We saw several patients with chronic gastric catarrh, dilatation of the stomach, and gastroptosis who felt the stomach oppressed and filled up.

From the foregoing observations we conclude that attention to dosage, evacuation of bowels, and diet (fluid or semifluid diet is necessary) are particularly important in the treatment of patients suffering from intestinal tuberculosis or from general stomach or intestinal disturbances.

GLANDULAR TUBERCULOSIS. The remedy manifests a wonderful effect on relatively early cases of glandular tuberculosis. In cases of lymphoma colli tuberculosum the swollen glands are at first still more swollen and the skin at the point of swelling is reddened; but in a few days these signs diminish gradually, and by the time of the next injection the glands usually have become somewhat smaller than before the treatment was begun. After the next injection they are again swollen, but less extensively so, and as the symptoms abate the glands show further contraction. After several treatments the glands were almost wholly absorbed. A patient at Hamadera may be cited as an example of typical reaction to the treatment. The swollen glands, originally as large as an egg, were almost totally absorbed after six successive injections.

It is important to say here that a somewhat larger dosage is necessary in the treatment of glandular tuberculosis. A patient at Osaka who had a marked lesion in the right lung, which extended through two whole lobes and swollen glands as large as dove's eggs on both sides of the neck, showed a remarkable improvement after three injections, the following doses being given: 4 c.c. at the first injection, 5 c.c. at the second, and 6 c.c. at the third. The multiple rales were wonderfully reduced, dulness almost disappeared, fever descended, and the body weight increased, while not the slightest influence could be detected on the swollen glands. After the fourth injection, when 7 c.c. were given, the glands became somewhat swollen, became painful to pressure, and were somewhat softened. On the fifth injection (6.5 c.c.), the same reactive signs were definitely noted, but as the pulmonary symptoms, which had practically disappeared, reappeared, the dose was reduced to 5 c.c., and this time no effect was observed. Since then, in spite of three successive injections, the glands remain quite unchanged. From this we may assume that it needs more than 6.5 c.c. to produce a beneficial effect upon glandular tuberculosis.

LARYNGEAL TUBERCULOSIS. Unfortunately the remedy seems to have very little effect on laryngeal tuberculosis.

GENERAL REACTIONS. *Fever.* The influence of the remedy upon fever varies very much, but in most afebrile cases without complication there is no rise in temperature. Occasionally a slight rise (0.5° C.) was observed, which disappeared usually on the following day. In slightly feverish cases the fever disappears in two or three days after injection. The temperature begins to rise before the next injection, which causes it again to fall. Repetition of the treatment brought a permanent afebrile condition after several injections. In favorable cases this result may be obtained by only one injection. We had little experience with highly feverish patients because we tried usually to bring the temperature down near normal, before beginning the treatment, by means of Ishigami's antituberculous serum, autovaccine cultivated from the sputum of the patient, or antipyretics. So far as our experience goes, however, the temperature is sooner or later brought down to normal or nearly so, though it does not fall immediately. In these cases we were particularly cautious about the size of the dose, for a large dose is quite likely to increase the fever, lower the general condition of nutrition, and bring on cachexia. We summarize the total results in febrile cases as follows:

AT TENNOJI.

Temperature.	1st stage.		2d stage.		3d stage.	
	Injections.	Per cent.	Injections.	Per cent.	Injections.	Per cent.
Raised . .	13	17.3	26	14.2	12	9.7
Lowered .	14	18.7	54	29.5	47	37.9
Unchanged .	48	64.0	103	56.3	65	52.4

AT HAMADERA.

Raised . .	21	26.9	66	18.0	27	16.9
Lowered .	11	14.2	55	15.0	60	37.7
Unchanged .	46	58.9	245	67.0	72	75.4

Pulse. No remarkable influence upon the bloodvessels was noted, though in not a few patients the rapidity of the pulse was somewhat reduced and the pulse became somewhat more regular. These phenomena are partly at least, attributable to the fact that the patient is always confined to bed and kept strictly at rest for a certain period.

Perspiration. In the great majority of cases we found the patients somewhat inclined to excessive perspiration. We recognized it in more than 50 per cent. of all patients.

AT TENNOJI.

	Number of patients.	Number of injections.	Number of patients sweated.	Number of injections after which sweating followed.	Percentage as to:	
					Patients.	Injections.
1st stage .	17	75	9	14	53.0	18.5
2d stage . .	36	183	20	36	55.5	19.7
3d stage . .	23	124	13	28	56.5	22.6
	76	382	42	79	55.3	20.6

AT HAMADERA.

1st stage .	21	78	2	3	9.5	3.8
2d stage . .	57	366	21	31	36.8	8.5
3d stage . .	29	109	19	28	65.5	16.5
	107	613	42	62	39.2	10.1

From this table it will be noticed that perspiration after the injection occurred much more frequently at Tennoji than at Hamadera. Especially is the difference noted in cases of the first stage. As our observations were made chiefly in summer, *i. e.*, from May to November, this result could be explained by the difference in temperature due to the respective locations of the two hospitals.[3]

Perspiration depends somewhat upon the dosage also. The greater the dose the more frequent the sweating. This relation may be clearly seen from the following table:

	Number of patients having frequent sweats.	Percentage.
Above 6.5 c.c.	40	53.2
Under 6.0 c.c.	5	6.5
Under 5.0 c.c.	10	13.0
Under 4.0 c.c.	11	14.3
Under 3.0 c.c.	10	13.0

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[3] Hamadera is situated on the seashore about ten miles south of Osaka, and is popular as a summer resort because of its relatively cool climate. Tennoji Hospital is situated in the south suburb of Osaka, the greatest industrial city in Japan, and having a notoriously hot climate. The ventilation of the hospital is not ideal.

Perspiration also bears some relation to the number of injections. It is most frequently met with at the first injection and gradually disappears in the course of succeeding injections. This is shown in the following table:

AT TENNOJI.

	1st stage.	2d stage.	3d stage.	Total.	Percentage.
1st injection . . .	7	18	11	36	46.1
2d " . . .	4	6	8	18	23.0
3d " . . .	2	6	4	12	15.4
4th " . . .	1	4	1	6	7.7
5th " . . .	0	1	1	2	2.6
6th " . . .	0	0	1	1	1.3
7th " . . .	0	1	1	2	2.6
8th " . . .	0	0	0	0	0
9th " . . .	0	0	1	1	1.3
10th " . . .	0	0	0	0	0
11th " . . .	0	0	0	0	0
Total	14	36	28	78	100.0

AT HAMADERA.

1st injection . . .	2	13	10	28	40.3
2d " . . .	1	6	8	15	24.3
3d " . . .	0	7	3	10	16.1
4th " . . .	0	1	3	4	6.5
5th " . . .	0	1	2	3	4.8
6th " . . .	0	0	1	1	1.6
7th " . . .	0	1	0	1	1.6
8th " . . .	0	1	0	1	1.6
9th " . . .	0	1	0	1	1.6
10th " . . .	0	0	1	1	1.6
11th " . . .	0	0	0	0	0
Total	3	31	28	62	100.0

In general the perspiration occurs most often in cases of the third stage, but there are many exceptions to this rule.

ACCESSORY EFFECTS. The accessory ill effects of this remedy, which are met with only in rare cases, may be summarized as follows:

(*a*) Headache and congestion. In a small number of cases (2 to 6 per cent.), headache and congestion were complained of, accompanied by slight fever and flushing of the face. These signs remained only a few days.

(*b*) Oppressive feelings in the chest are often complained of by nervous and sensitive patients or when excessive dosage is applied. In most cases this symptom vanished within twenty-four hours, and it rarely lasted more than two or three days.

(*c*) Discomfort in stomach and intestines are felt by those who are suffering from intestinal tuberculosis or from acute or chronic digestive disturbances. This disappears after two or three days. Gastralgia was also noted in some cases.

GENERAL CONDITION AFTER INJECTION. *Subjective.* In many instances no remarkable change in subjective condition is noted. In not a few cases, however, the patient feels quite comfortable and at ease, as if he suddenly became quite free from the illness. This feeling is most common after the first injection, and by the third or fourth injection it is no longer noticed.

Changes in Nutrition. As already repeatedly described all patients are kept at rest for three days after injection, and during this period most of them lost some body weight. The patient was weighed on the day of injection, five days later, and not again until the next injection, two weeks later. We observed that on the fifth day the weight is somewhat reduced in most cases, and only in a small number of cases was it increased. On the day of the next injection, however, the loss is not only quite recovered, but often there is a definite increase in weight. There seems to be a direct relation between body weight and general improvement, *i. e.*, those who gain in body weight are usually much improved while those who lose weight are worse. Loss of weight was almost constant at first when larger doses were used. At that time even those who were strikingly improved lost weight and could not regain it by the time of the next injection. Since the reduction of dosage, however, increase of weight and general improvement run parallel.

We sum up the total results with regard to body weight in the following table:

AT TENNOJI.

	1st stage.	2d stage.	3d stage.	Total.
Weight increased:				
Number of patients	9	18	16	53
Percentage	52.9	77.8	69.6	66.8
Average increase per person . .	2.006 kg.	2.108 kg.	2.108 kg.	2.130 kg.
Weight decreased:				
Number of patients	8	8	7	23
Percentage	47.1	22.2	30.4	33.2
Average decrease per person . .	0.363 kg.	1.244 kg.	1.122 kg.	0.9 kg.
Weight constant	0	0	0	0
Maximum increase	5.4 kg.	6.4 kg.	4.35 kg.	
Maximum decrease	0.85 kg.	2.2 kg.	3.3 kg.	

AT HAMADERA.

Weight increased:				
Number of patients	18	44	20	82
Percentage	85.7	77.2	68.9	76.6
Average increase per person . .	1.811 kg.	2.645 kg.	2.355 kg.	2.391 kg.
Weight decreased:				
Number of patients	2	10	8	20
Percentage	9.5	17.6	27.6	18.7
Average decrease per person . .	0.9 kg.	1.22 kg.	2.355 kg.	1.643 kg.
Constant (percentage)	4.8	5.2	3.5	4.7
Maximum increase	6.4 kg.	13.2 kg.	5.5 kg.	
Maximum decrease	1.5 kg.	3.0 kg.	4.8 kg.	

It is easy to see from the table how remarkable the results are. It is to be noted that the results are in general better at Hamadera than at Tennoji. We may point out the following factors to explain the difference:

1. The climate in Hamadera is much better than in Tennoji.
2. The equipments are also much better at Hamadera.
3. The patients treated at Hamadera are usually from a class living under better social and economic conditions than those at Tennoji.
4. Patients stay much longer in the Sanatorium at Hamadera than at Tennoji.

We conclude therefore that although the favorable results of the treatment upon nutrition are remarkable, they cannot be attributed to the effect of the remedy alone. The open-air treatment, heliotherapy, hydrotherapy, dietetic treatment, and other routine treatments play an important part in the results.

Next to the increase in body weight, the improvement in the appearance is most remarkable. The anemic or cachectic and exhausted appearance which is so common in patients of advanced stages, with high fever, and especially in those suffering from intestinal tuberculosis, is in most cases wonderfully improved after several injections if the proper dosage has been chosen. The improvement in countenance may come before the restoration of nutrition and the disappearance of fever.

Cough and Expectoration. No remarkable change occurs on the day of injection. On the next day there is an increase of coughing and expectoration in many cases, followed by a gradual decrease. In some cases coughing and expectoration diminish immediately. There are some also in whom no change occurs.

Appetite. In patients suffering from gastro-intestinal disturbances the appetite is more or less affected, sometimes totally lost. This is rare, however, and in a great many cases the appetite remains almost or quite unaffected.

Lung Capacity. To measure the lung capacity we used Hutchinson's spirometer. This apparatus does not always give exact results. No definite conclusions can be drawn, therefore, and we use the measurements only as supplementary material. Results vary widely, showing no definite correspondence with other symptoms, yet in general there seems to be a favorable effect on lung capacity.

Laryngeal Tuberculosis. So far as our limited experience goes the remedy has a stimulating effect in laryngeal tuberculosis, that is, the surrounding parts of the ulcer become hyperemic and reddened for two or three days. Later the redness disappears, the surface becomes granulous in appearance, and the base of the ulcer is somewhat cleansed from caseous masses.

Intestinal Tuberculosis. Further experience is needed before any estimation can be made with regard to the therapeutic value of cyanocuprol for intestinal tuberculosis. As already mentioned the unfavorable reaction can be avoided in a measure if special attention is given to (1) dosage, (2) diet, (3) evacution of bowel contents. We treated several cases without causing reaction.

Influence upon Tubercle Bacilli. The results of the research vary very widely with respect to the change in number and form of tubercle bacilli in the sputum. We may classify the results as follows:

1. Immediately after the injection the number of bacilli is increased. Later it decreases and in favorable cases the bacilli disappear in a few days.
2. A gradual decrease in number of bacilli takes place without the initial increase.
3. In some cases when the examination of the sputum has been negative it becomes positive after one or two injections, and in the further course of the treatment it becomes again negative or remains positive continuously.
4. The bacilli at first disappear but are found again later.
5. No influence is observed.

We could confirm the facts reported by Koga in some cases, but the time of appearance of such forms as he found does not always bear the same relation to the time of injection. Moreover, such forms may often be seen in the sputa of chronic and cavernous cases. It is impossible, therefore, to decide whether or not such changes are actually caused by this treatment. On the other hand, we saw a patient in whom the sputum had been constantly negative suddenly spit out just after the third injection sputum containing numerous bacilli corresponding to No. X of Gaffky's table. The morphological changes had been noted more often before the reduction of dosage.

Provided the influence be a real one the question whether or not it is the direct effect of the preparation (in the sense of Ehrlich's chemotherapy) still requires investigation.

Hemoptysis. If proper dosage is given the danger of causing hemoptysis is not very great. At Tennoji, among 76 patients and 382 injections, we saw bloody sputum once only in each of 13 patients, and at Hamadera among 107 patients and 613 injections only once in each of 16 patients. The danger is somewhat greater when patients have a history of hemoptysis unless the injections are small and are not given too close to the time of hemoptysis.

At the time when we were still giving large doses, 7 c.c. and 7.5 c.c. were successively given to a patient who had expectorated blood once long before. The symptoms were so much improved that we gave him 8 c.c. at the next injection, attempting to kill all of the bacilli at one blow. On the day after injection, to our great astonishment, the patient raised more than 300 c.c. of blood at one time, the general condition subsequently becoming much worse. The sputum continued bloody for more than a month, so that we were compelled to discontinue the treatment. This case was one of those which led us to the conclusion that the dose should be reduced even if the healing process was thereby retarded. There was a marked decrease in the number of occurrences of this sort after reduction of dosage, with no decided effect upon the efficacy of the drug. Since this bitter experience we have been particularly cautious in cases in which there is any history of hemoptysis. The period of rest is prolonged for such patients and narcotics are prescribed. The intravenous injection of calcium sometimes serves the purpose of a narcotic quite remarkably.

Relation to von Pirquet Reaction. At the spot where the von Pirquet inoculation had previously been made reddening becomes intense, induration increases in degree, and extension after the injection of cyanocuprol. The reaction becomes more intense with each successive injection until after the third to fifth, when the sensitiveness gradually decreases. It is noteworthy that in highly weakened cases, when the reaction ordinarily remains negative, it became positive after several injections.

Indication and Contra-indication. The relatively early cases, those in the first stage, are particularly indicated. Among patients of the second stage the treatment is indicated for those who have a slowly progressing limited lesion. If the affection is widespread or the change quite extensive, it requires great care to select suitable cases for the treatment.

Very much advanced cases, whose general condition is much weakened, or the breathing surface greatly restricted, are contra-indicated. Highly feverish cases, those in which the von Pirquet reaction is negative, or where there has been hemoptysis, are doubtful. Those who have advanced intestinal or laryngeal affections are unfitted for treatment. Patients suspected of general miliary tuberculosis or tuberculous meningitis are certainly contra-indicated. As for cases with recent pleuritis or peritonitis it is better to wait until the first inflammatory process is arrested.

Menstruation is not at all affected. We have no experience with pregnancy.

We very often combined a calcium salt with cyanocuprol to prevent hemoptysis or to prevent the reaction without apparent effect on the healing tendency of the latter. Five to ten c.c. of 5 per cent. solution of calcium chlorid is given intravenously.

Opsonin index is not in most cases increased after the injection.

The content of hemoglobin is increased after several injections.

The number of leukocytes is increased immediately after the injection, but after four to six days decreases again to the original number.

Better results with cyanocuprol are usually obtained in patients previously treated with tuberculotoxoidin.

SUMMARY. 1. Cyanocuprol is very effective in all cases of the first stage. In the majority of cases of the second stage it is also effective. With patients of the third stage it many manifest its effect to a certain extent if favorable cases. are selected and proper dosage is given.

2. The effect of cyanocuprol cannot be called strictly chemotherapeutic. It shows in some respects a strong resemblance to tuberculin.

3. The essentials of the treatment with cyanocuprol lie in finding the proper dosage for each patient. If the individualization, which is especially important with this remedy, is properly carried out its value is indeed remarkable, surpassing all other remedies ever tried.

4. The combination of calcium prevents violent reactions and does not affect the efficacy of the drug.

5. The combination of immune therapy and sanatorium treatment is necessary.

6. The question of the duration of the treatment is an important one. According to our own experience if the patient is not improved after two or three injections, or is weakened, the dosage should be reduced or the interval extended. If this brings no improvement the treatement must be given up. Even in favorable cases, when the results are good after each injection, the treatment is best interrupted between the fifth and sixth and eleventh and twelfth injections, for at these times the condition is most improved. If treatment is continued in such cases there will be no benefit from it; instead there may be a return of previous symptoms and the patient's condition may become hopeless.

In conclusion, it is our pleasant duty to pay our best respects to Dr. Koga, and also to express our hearty thanks to Doctors Takagi, Imai, Yukawa, Honda, and Yano for their kind assistance throughout the whole period of our observations.

VAGINAL METASTASES OF HYPERNEPHROMA.

By George Gellhorn, M.D., F.A.C.S.,

ASSOCIATE IN GYNECOLOGY, WASHINGTON UNIVERSITY, ST. LOUIS, MISSOURI.

THE urinary and genital apparatus in the female are closely connected both topographically and developmentally. In disease this intimate relationship becomes even more apparent. I need but mention the frequent occurrence of pyelitis in pregnancy, the effect upon the bladder of an incarcerated retroflexion of the gravid uterus, the role of cystocele in the etiology of genital prolapse, the relations